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Diagnosis of pulmonary embolism

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Summary

Pulmonary embolism is the third cause of mortality by cardiovascular disease after coronary artery disease and stroke, and its incidence is around 1/1000 per year. During the last two decades, many different non-invasive diagnostic tests have been developed and validated. For hemodynamically stable outpatients, the diagnosis of acute pulmonary embolism mainly rests on the sequential use of clinical assessment, D-dimer measurement and multidetector CT. In patients with a contraindication to CT, lower limb venous ultrasonography and ventilation-perfusion scintigraphy remain valid options. Massive pulmonary embolism is a distinct clinical entity with a specific diagnostic approach. In unstable patients with suspected pulmonary embolism, echocardiography should be the initial test.

Introduction

Pulmonary embolism (PE) is the third cause of mortality by cardiovascular disease after coronary artery disease and stroke. It has been estimated that over one million venous thromboembolic (VTE) events or deaths occur each year in six large European countries. Three quarters of VTE-related deaths are due to hospital-acquired VTE, which therefore represents a major health concern [1]. PE is difficult to diagnose because of variable clinical manifestations and poor sensitivity and specificity of symptoms and signs. However, considerable progress has been made in the workup of patients with clinically suspected PE with the advent of diagnostic instruments such as plasma D-dimer measurement, lower limb venous compression ultrasonography and computed tomography pulmonary angiography (CTPA). Moreover, well-validated, rational and cost-effective diagnostic strategies are now available [2].

Clinical presentation

None of the various presenting symptoms of PE is specific to this disease. In 65% of patients, PE is evoked because of pleuritic chest pain. Isolated shortness of breath, usually acute but sometimes

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slowly progressive and without an obvious alternative cause, is reported in about 20% of patients [3]. Syncope or shock are a rare clinical presentation of PE (less than 10%). Finally, PE may be discovered in the absence of a clinical suspicion on CT scans performed for other reasons, mostly cancer staging and follow-up.

Diagnostic strategies

Clinical probability of pulmonary embolism

Sensitivity and specificity of clinical symptoms, signs and abnormalities of blood gases, chest X-ray and electrocardiogram in suspected PE are low when considered singly. Nevertheless, these findings can be combined effectively by clinicians to estimate the patient's probability of having PE, either implicitly or by prediction rules [4,5]. Both ways of assessing clinical likelihood of PE allow a fairly accurate stratification of patients into two (PE unlikely or PE likely) or three categories (low, intermediate or high clinical probability) corresponding to an increasing prevalence of the disease [6,7]. The vast majority of patients have a low or intermediate clinical probability of PE (around 90%) or belong to the PE unlikely category (around 70%). *Table I* shows the two most widely used prediction rules for PE in their original and simplified versions. The Wells rule [5] has been widely validated and can be applied to both out- and inpatients, but it requires a subjective judgment on the probability of an alternative diagnosis, which reduces its interobserver reliability. The revised Geneva score [4] has only been validated in outpatients, but is entirely based on objective criteria. Two recent meta-analyses confirmed the validity of the original and simplified versions of both the Wells and the revised Geneva rules [8,9]. These rules have also been formally evaluated by a direct prospective comparison that showed similar diagnostic performances [10].

D-dimer

Plasma D-dimer, a degradation product of cross-linked fibrin, has been extensively investigated in the last 25 years in the setting of VTE diagnosis [11]. Plasma D-dimer levels increase in presence of an acute clot. Hence, a D-dimer level below a certain prespecified cut-off, referred to as "negative" D-dimer, renders acute PE unlikely. However, D-dimer has a low specificity and is not useful for confirming PE. There are numerous available D-dimer assays with different characteristics [11]. The quantitative ELISA or ELISA-derived assays have a sensitivity above 95% at the usual cut-off level of 500 µg/L. They can therefore be used to rule out PE in patients with either low or moderate probability of PE (using three-level scores) or patients classified as PE unlikely (using two-level scores). In the emergency department or in the outpatient setting, a negative ELISA D-dimer can exclude PE without further testing in approximately 30% of patients [6,7]. Outcome studies have shown that the three-month thromboembolic risk was very low (< 1%) in patients left untreated based on a negative ELISA D-dimer test result [12]. Quantitative latex-derived assays and a whole-blood agglutination assay have lower sensitivity in the range of 85 to 90% [11]. Using the two-level Wells rule, moderately sensitive assays are still safe to exclude PE in patients categorized as PE unlikely [7]. However, if a three-level clinical prediction rule is used, the lower sensitivity D-dimer tests only allow to safely rule out PE in patients with a low clinical probability. The diagnostic yield of D-dimer is linked with the false-positive rate that varies according to patient characteristics, for example patient age [13]. As a result, the clinical usefulness of the test, that is the proportion of patients with a D-dimer level below the predetermined cut-off value in whom the diagnosis of PE may be ruled out by the test, is reduced [14]. Recently, the value of a progressive D-dimer cut-off adjusted to age was derived and retrospectively validated (age-adjusted cut-off, in µg/L, equals patient's age multiplied by 10 in patients aged 50 years or more; usual 500 µg/L cut-off value in younger patients) [14]. Using the age-adjusted D-dimer cut-off would have increased the diagnostic yield by about 20% without increasing the false negative rate. This approach has been formally evaluated in a large prospective outcome study [15] in which all patients with a non-high clinical probability (three-level rule) or belonging to the PE unlikely category (two-level rule) with D-dimer levels below the age-adjusted cut-off were left untreated with no further diagnostic testing. In this multicenter European study including 3346 patients, 817 patients (28%) had a D-dimer level below the conventional 500 µg/L cut-off, and an additional 337 patients (12%) had a D-dimer level above 500 µg/L but below their age-adjusted cut-off. The three-month thromboembolic risk was below 1% and similar in both groups. In patients aged 75 years and more, the age-adjusted cut-off increased the proportion of patients in whom PE could be safely ruled out by D-dimer five-fold [15]. Using the age-adjusted D-dimer cut-off thus significantly increases the diagnostic yield of D-dimer in elderly patients.

D-dimer is also more often elevated in patients with cancer, in hospitalized patients and during pregnancy. Deciding whether measuring D-dimer is still worthwhile in these situations remains a matter of clinical judgment.

In summary, a "negative" D-dimer result by a highly sensitive assay safely excludes PE in patients with a low or moderate clinical probability, while a moderately sensitive assay excludes PE in patients with a low clinical probability or classified as PE unlikely. The use of an easily remembered age-adjusted D-dimer cut-off value has great potential to further reduce the number of unnecessary imaging tests in older patients with suspected PE.

Lower limb venous compression ultrasonography

Lower limb venous compression ultrasonography has become the standard test for diagnosing deep venous thrombosis (DVT)